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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/695,769	10/25/2000	Darwin J Prockop	57616-5018US1	4022
23973 7590 04/20/2007 DRINKER BIDDLE & REATH ATTN: INTELLECTUAL PROPERTY GROUP ONE LOGAN SQUARE 18TH AND CHERRY STREETS PHILADELPHIA, PA 19103-6996			EXAMINER HAMA, JOANNE	
			ART UNIT 1632	PAPER NUMBER
SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE		
3 MONTHS	04/20/2007	PAPER		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

<b>Office Action Summary</b>	<b>Application No.</b> 09/695,769	<b>Applicant(s)</b> PROCKOP ET AL.	
	<b>Examiner</b> Joanne Hama, Ph.D.	<b>Art Unit</b> 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 25 January 2007.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-12, 14-19, 21-26 and 31-36 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-12, 14-19, 21-26 and 31-36 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date: _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date: _____   | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

Applicant filed a response to the Non-Final Action of August 8, 2006 on January 25, 2007. Claims 1, 12, 21, 24, 31, 32 are amended. Claims 13, 20, 27-30, 37-41 are cancelled.

Claims 1-12, 14-19, 21-26, 31-36 are under consideration.

### **Withdrawn Rejections**

#### **35 U.S.C. § 112, 1<sup>st</sup> parag. Enablement**

Applicant's arguments, see pages 8-10, filed January 25, 2007, with respect to the rejection of claims 1, 22-29 have been fully considered and are persuasive.

With regard to the Examiner raising the issue that Kuznetsov et al. teach "serum-free medium" (Office Action, August 8, 2006, pages 5-6), Applicant indicates that "growth medium" was described in the specification (page 18, lines 1-2) as a composition of matter that comprises the minimal nutrients to sustain proliferation and that on page 20, line 12, growth medium can contain one or more mammalian serum. Applicant also indicates that the claims have been amended to recite, "growth medium comprising a mammalian serum." In response, this is persuasive and the rejection as it applies to this issue is withdrawn.

With regard to the claims being drawn to an addition of a "factor" (Office Action, August 9, 2006, pages 6-7), Applicant indicates that "growth factor" recited in claims 22 and 23 are fully enabled. Applicant indicates that specification adequately supports the use of a growth factor, such as fibroblast growth factor, a platelet derived growth factor,

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an insulin growth factor, or an endothelial growth factor to supplement the medium (specification, page 20) (Applicant's response, page 10, 2<sup>nd</sup> parag.). In response, this is persuasive and the rejection as it applies to this issue is withdrawn.

With regard to the claims being drawn to a "factor," as they apply to claims 24-29, Applicant indicates that the claims have been amended such that conditioned medium is added to the growth medium (Applicant's response, page 10, 4<sup>th</sup> parag.). In response, deletion of the phrase indicating that a factor present in condition medium overcomes the rejection indicated in the Office Action, August 9, pages 6-7). Thus, the rejection as it applies to this issue is withdrawn.

**35 U.S.C. 112, 1<sup>st</sup> parag. Written Description**

Applicant's arguments, see pages 10-11 of Applicant's response, filed January 25, 2007, with respect to the rejection of claims 1, 22-29 have been fully considered and are persuasive. Applicant indicates that the rejection is not applicable to claims 22 and 23 as the specification adequately discloses the use of a growth factor, such as fibroblast growth factor, a platelet derived growth factor, an insulin growth factor, or an endothelial growth factor to supplement the medium (specification, page 20) (Applicant's response, page 11, 2<sup>nd</sup> parag.). In response, this is persuasive and the rejection as it applies to claims 22 and 23 is withdrawn.

With regard to the use of the word, "factor" (claim 24), Applicant indicates that the claim has been amended to indicate that conditioned medium is added to the growth medium. This is persuasive and the rejection as it applies to this issue is withdrawn.

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The rejection of claim 1, 22-26 is withdrawn. The rejection of claims 27-29 is withdrawn as the claims have been cancelled.

**35 U.S.C. 103(a)**

Applicant's arguments, see pages 12-16 of Applicant's response, filed January 25, 2007, with respect to the rejection of claims 1-12, 14-29, 31-36, as being obvious by Huang, have been fully considered. It is noted that the rejection of claims 1-12, 14-19, 21-26, 31-36 is withdrawn as the claims have been amended to comprise a specific limitation that plating human marrow stromal cells at 50 cells or fewer per square centimeter results in a greater total number of cells than marrow stromal cells plated more than 50 cells per square centimeter. The rejection is withdrawn because Sekiya et al. (see Enablement, below) teaches that this specific limitation is not enabled. It is noted that should Applicant remove this limitation, Huang will be reapplied because Huang teaches the same steps as those claimed. It is noted that the rejection of claims 20, 27-29 are withdrawn as the claims have been cancelled.

Applicant's arguments, see pages 16-17 of Applicant's response, filed January 25, 2007, with respect to the rejection of claims 1, 22-29, 31-36 as being obvious over Huang et al. in view of Kuznetsov et al., Azizi et al., Greenberger, and Prokop have been fully considered. It is noted that the rejection of claims 1, 22-29, 31-36 is withdrawn as the claims have been amended to comprise a specific limitation that plating human marrow stromal cells at about 50 cells or fewer per square centimeter results in a greater total number of cells than marrow stromal cells plated more than

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about 50 cells per square centimeter. The rejection is withdrawn because Sekiya et al. (see Enablement, below) teaches that this specific limitation is not enabled. It is noted that should Applicant remove this limitation, Huang et al., Kuznetsov et al., Azizi et al., Greenberger, and Prokop will be reapplied because Huang et al., in view of Kuznetsov et al., Azizi et al., Greenberger, and Prokop teach the same steps as those claimed. The rejection of claims 1, 22-26, 31-36 has been withdrawn. It is noted that the rejection of claims 27-29 is withdrawn as the claims have been cancelled.

### **New/Maintained Rejections**

#### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 14-19, 21-26, 31-36 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 1, 24, 31, 32 have been amended to indicate that the claimed method of plating isolated human marrow stromal cells at an initial density of less than about 50 cells per square centimeter of growth surface results in a greater total number of cells to

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be obtained compared to the total number of cells obtained from plating and replating cells that have been plated at an initial density of more than about 50 cells per square centimeter. Applicant indicates that support for the amendment is found throughout the specification and indicates, for example, that Example 2 provides support (Applicant's response, page 8, under Amendments to the Claims). In response, the Examiner has looked through the specification and has not found support that at a particular density (i.e., 50 cells per square centimeter), that cells plated at a density lower than 50 cells per square centimeter yield more cells than cells plated at a density higher than 50 cells per square centimeter. The closest teaching in the specification that might be related to the amendments of claims 1, 24, 31, 32, is that the specification (Example 2) teaches that human marrow stromal cells (MCS) were plated 3 cells per square centimeter (specification, page 36, 1<sup>st</sup> parag. under "Expansion of MCS") and indicates a particular-fold increase of cells obtained 10 and 14 days after plating (specification, Table 2). The specification also teaches that prior art techniques for expanding MSCs in culture at a density of about 5,000 cells per square centimeter and then growing the cells for about 2 weeks results in about a 3-fold expansion of MSC cell number (specification, page 38, 3<sup>rd</sup> parag.). It is noted that this teaching indicates x-fold expansion, however, it does not teach total number of cells obtained. As such, the specification does not specifically teach that 50 cells per square centimeter is a critical density at which MSCs should be plated at such that the total number of cells obtained is greater than that of cells plated at a higher density.

It is noted that the Examiner has also looked at Example 3 of the specification, which appeared to be most relevant to claim 24. While Example 3 teaches the addition of conditioned media to MSCs, the specification does not teach that 50 cells per square centimeter as a particular density to use to plate cells such that the number of cells obtained using this density is greater than that obtained from cells plated more than 50 cells per square centimeter.

It is also noted that the Examiner has looked at Examples 1 and 2 of the specification, which appeared to be most relevant to claims 1, 31, 32. As indicated above, Example 2 does not teach that 50 cells per square centimeter as a particular density to use to plate cells such that the number of cells obtained using this density is greater than that obtained from cells plated more than 50 cells per square centimeter. It is noted that Example 1 teaches how to obtain mononuclear cells (specification, page 29, line 15); however, no guidance was provided about plating density and obtaining greater numbers of cells, depending on the plating density.

Claims 1-12, 14-19, 21-26, 31-36 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 24, 31, 32 have been amended to indicate that plating and replating isolated human marrow stromal cells (MSC) at an initial density of about 50 cells or



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fewer per square centimeter results in a greater total number of cells to be obtained compared to the total number of cells obtained from plating and replating cells plated at an initial density of more than 50 cells per square centimeter. The claimed invention is not enabled because post-filing art provides guidance that is contrary to what is claimed. Sekiya et al., 2002, Stem Cells, 20: 530-541 teach that when MSCs are plated at 1000 cells per square centimeter, about 1.6 million cells are obtained after 12 days in culture; cells plated at 10 cells per square centimeter yield 0.3 million cells (Sekiya et al., page 533, 2<sup>nd</sup> col., 2<sup>nd</sup> parag. and Fig. 2B). As such, Sekiya et al.'s teaching is contrary to what is claimed. As this issue applies to the instant invention, Sekiya et al.'s post-filing teaching indicates an artisan cannot plate cells at densities of 50 cells or fewer per square centimeter and expect that the number of cells obtained from the plating is more than that obtained from cells plated more than 50 cells per square centimeter.

Thus, the claims are rejected.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12, 14-19, 21-23, 25, 26, 31-36 are newly rejected and claim 24 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons of record, August 8, 2006. It is noted that Applicant has addressed the rejections as they apply to claims 1-12, 14-19, 21-23, 25, 26, 31-36, and

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thus have overcome the rejections of record, see below. However, Applicant's amendments raise a new issue of rejection and the rejection is thus as follows.

Response to Applicant's response, January 25, 2007, will be provided following the new issue of rejection.

Claim 1, lines 5-6, uses the phrase, "50 cells per square centimeter of growth factor." It is unclear what this means. Did Applicant intend to mean "growth surface?" Or, did Applicant intend to mean that the cells were plated 50 cells per square centimeter per a particular concentration of growth factor in the media? Claims 24, 31, 32 use the same phrase and are also rejected. Claims 2-12, 14-19, 21-22 depend on claim 1 and are included in the rejection. Claims 25, 26 depend on claim 24 and are included in the rejection. Claim 33-36 depend on claim 32 and are included in the rejection.

Applicant's arguments, see pages 11-12, filed January 25, 2007, with respect to the rejections of claims 1-12, 14-29, 31-36 have been fully considered and are persuasive in part.

With regard to the limitation, claim 24, lines 8-9, "the proliferated isolated marrow stromal cells (Office Action, August 8, 2006, page 11)," Applicant indicates that that there is sufficient antecedent basis for the term (Applicant's response, January 25, 2007, page 12). Applicant indicates that claim 24 recites a method of enhancing *in vitro* proliferation of isolated human marrow stromal cells grown on a surface and that the phrase, "the proliferated isolated marrow stromal cells" refers to the cells plated at an initial density of less than about 50 cells per square centimeter of growth surface prior to

replating the cells. In response, this not persuasive because nothing preceding the phrase "proliferated isolated marrow stromal cells" indicates that the population of cells had proliferated. For example, note that the claim can be readable such that the cells plated in the dish are dormant. Thus, it is not entirely clear what population of cells had "proliferated." As such, the rejection as it applies to the claim remains.

With regard to the rejection of claim 1, wherein step 3 was unclear as to what was meant by a "growth surface," Applicant indicates that claim 1 has been amended to indicate that the growth surface is a "second" growth surface (Applicant's response, page 11). It is noted that a similar rejection had been applied to claims 24, 31, 32. Applicant's amendment is persuasive and the rejection as it applies to claims 1-12, 14-19, 21-26, 31-36 is withdrawn. It is noted that the rejection of claims 20, 27-30 is withdrawn as the claims have been cancelled.

With regard to the rejection of claim 12 for antecedent basis for using the term, "second growth surface," Applicant indicates that claim 1 has been amended to indicate that the growth surface is a "second" growth surface (Applicant's response, page 11). Applicant's amendment is persuasive and the rejection as it applies to claims 12, 14-19 is withdrawn. (It is noted that claim 13 had been rejected, Office Action, page 10; however, claim 13, May 18, 2006, was cancelled.)

With regard to the rejection of claim 12, wherein line 3 recited the word, "surfact," Applicant indicates that claim 12 has been amended to "surface." This is persuasive and the rejection as it applies to claims 12, 14-19 is withdrawn. (It is noted that claim 13

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had been rejected, Office Action, page 10; however, claim 13, May 18, 2006, was cancelled.)

### ***Conclusion***

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JH

ANNE M. WEHBE' PH.D  
PRIMARY EXAMINER

